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Health and Environmental Effects Profile for N,N-Dimethylurea

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16. ABSTRACT

The Health and Environmental Effects Profile for N,N-dimethylurea was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for N,N-dimethylurea.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR N,N-DIMETHYLUREA

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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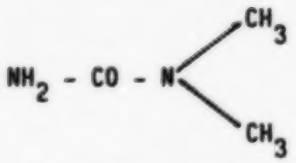
1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The compound N,N-dimethylurea is also known as 1,1-dimethylurea and asymmetrical dimethylurea (Weast, 1980; Von Kreybig et al., 1969). It has the following chemical structure:



The molecular formula for this compound is $C_3H_8N_2O$ and its molecular weight is 88.1. The Chemical Abstract Service (CAS) Registry number for N,N-dimethylurea is 598-94-7.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

N,N-Dimethylurea is a colorless crystalline solid at ambient temperature and has the following physical properties:

Melting point:	182°C (Weast, 1980)
Density (temperature unspecified):	1.255 g/cm³ (Weast et al., 1980)
Solubility in water:	soluble (Weast, 1980)
Solubility in other solvent:	soluble in ethanol and chloroform (Weast, 1980)

The chemical properties of this compound are not known with certainty; however, based on the properties of urea, it can be predicted that at high concentrations N,N-dimethylurea may react with strong acids to produce the corresponding salts. Unlike urea, it may not react with hydrogen peroxide (Heikkila and Cabbat, 1978) but may react with formaldehyde without forming cross-linked polymers.

1.3. PRODUCTION DATA

The 1977 U.S. EPA TSCA production file lists American Bio-Synthetics Corp., Milwaukee, WI, as a past producer of this chemical in the United States. According to SRI (1983), RSA Corp., Ardsley, NY, is the only present producer of dimethylurea (isomers unspecified) in the United States. It is likely that N,N-dimethylurea is produced only in small quantities.

1.4. USE DATA

No information pertaining to the use of this specific chemical could be found in the literature. The isomeric compound, N,N'-dimethylurea (1,3-dimethylurea), however, is used as an intermediate in the synthesis of drugs (Hawley, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Virtually no information regarding the fate and transport of this compound in any environmental medium is available. Based on the environmental reactivity of similar compounds, some predictions about the fate and transport of this compound can be made.

Given the lack of vapor pressure data, it is difficult to predict the physical state in which N,N-dimethylurea may predominate in the environment. The two most likely processes responsible for the removal of N,N'-dimethylurea in air are reactions with OH· radicals and NO_x. Neither of these reactions has been studied comprehensively. Heikkila and Cabbat (1978) reported that the rate constant for dimethylurea (isomer unspecified) reaction with hydroxyl radical is 2.7×10^9 M^{-1} sec^{-1}. If this rate constant value of 4.48×10^{-12} cm^3 $molecule^{-1}$ sec^{-1} is combined with the average urban atmospheric OH· concentration of 3×10^6 molecules cm^{-3} (Harris and Pitts, 1983), the half-life for N,N-dimethylurea will be ~15 hours. Since N,N-dimethylurea is an amine, its presence in the air raises the possibility of formation of nitrosamines or nitramines upon reaction with oxides of nitrogen in air. Nitrosamines may not be stable in air (Pitts et al., 1978).

In ambient aquatic media, peroxy radicals are not expected to cause significant reduction of N,N-dimethylurea concentration (Heikkila and Cabbat, 1978). This compound may, however, undergo slow hydrolysis in aquatic media (Mavrovic, 1970). Based on the information available for urea (Verschueren, 1983), N,N-dimethylurea is likely to undergo biodegradation in river water.

It is expected that this compound will undergo significant biodegradation in soils, since its probability of biodegradation in river water is high. Considering its water solubility, leaching of this compound from soil remains a distinct possibility.

3. EXPOSURE

Pertinent monitoring data regarding N,N-dimethylurea were not located in STORET or elsewhere.

4. PHARMACOKINETICS

4.1. ABSORPTION

Pertinent data regarding the absorption of N,N-dimethylurea were not located in the available literature.

4.2. DISTRIBUTION

No information relating to the distribution of N,N-dimethylurea in mammals was found in the available literature; however, Cohen and Bangham (1972) have indicated that N,N-dimethylurea rapidly diffuses across membranes of cholesterol-containing liposomes. Distribution to all tissues is, therefore, likely to be rapid and extensive.

4.3. METABOLISM

Dar (1975) administered [^{14}C]N,N-dimethylurea (225 µg/kg or 100 mg/kg) to female New Zealand rabbits and female Wistar rats by intraperitoneal injection in an aqueous medium. They concluded that N,N-dimethylurea undergoes stepwise demethylation, leading to the formation of methylurea and urea. This conclusion was based on the observation of metabolites in the urine (Section 4.4.).

4.4. EXCRETION

The only study located which measured the excretion of N,N-dimethylurea or its metabolites was that of Dar (1975) (vide supra). Radioactivity, as $^{14}CO_2$, appeared very quickly in the expired air of rabbits, with ~50% of the total $^{14}CO_2$ excreted appearing within the first 6 hours. Excretion of $^{14}CO_2$ continued during the next 18 hours of observation, but at a slower rate. The same pattern was observed in rats, but the initial rates were higher, with ~80% of the total excreted $^{14}CO_2$ detected in the first 6 hours. In both species, excretion in the expired air accounted for 4-12% of the total dose, and urinary excretion, predominately as methylurea, accounted for an additional 73-90% of the dose within 24 hours after dosing.

At the higher dose, respiratory excretion was reduced by ~50% and urinary excretion increased by ~6%. Dar speculated that the decreased excretion of respiratory $^{14}CO_2$ with a dose of 100 mg/kg was due to either feedback inhibition or repression of enzyme synthesis.

5. EFFECTS

5.1. CARCINOGENICITY

The English summary published at the end of a German paper (Sander, 1971) indicated that N,N-dimethylurea was carcinogenic when administered orally with nitrite. A closer examination of the paper, however, disclosed that the compound used was N,N'-dimethylurea. Thus, no study of the carcinogenicity of N,N-dimethylurea was located in the available literature.

5.2. MUTAGENICITY

Pertinent data regarding the mutagenicity of N,N-dimethylurea were not located in the available literature.

5.3. TERATOGENICITY

Von Kreybig et al. (1969) administered N,N-dimethylurea (1000 mg/kg) to unspecified numbers of pregnant CD or BD IX rats. The gestation day on which the compound was administered was not stated, but was probably between days 10 and 14, based on comparison with other tests reported in the same paper. No effect on embryo development was reported; however, details of the pathological examination were not given. N,N'-Dimethylurea, trimethylurea and tetramethylurea produced a number of terata, including umbilical hernia, dropsy, defects in the extremities and cauda, growth retardation and fetal death. No mention was made of the route of administration of these compounds.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects of N,N-dimethylurea were not located in the availabe literature.

5.5. CHRONIC AND SUBCHRONIC EFFECTS

Pertinent data regarding the subchronic or chronic effects of N,N-dimethylurea were not located in the available literature.

5.6. OTHER RELEVANT INFORMATION

The acute oral LD_{50} for rats has been reported to be >2000 mg/kg (Von Kreybig et al., 1969). Shikinami et al. (1930) reported the induction of hypoglycemia by N,N-dimethylurea (dose and species not given) and stated that administration of this chemical to diabetics resulted in a decrease in glucosuria. Haas (1947) reported that N,N-dimethylurea was a strong diuretic in the rat (dose not specified).

N,N-Dimethylurea has been demonstrated to be a competitive inhibitor of adenosine deaminase (Ronca and Ronca-Testoni, 1969) but did not induce P-450 in adult or weanling female rats (Kinoshita and DuBois, 1970). This compound is able to convert cytochrome P-450 to cytochrome P-420 (Ichikawa et al., 1968; Ichikawa and Yamano, 1967) in vitro; however, this observation has no obvious biological significance.

6. AQUATIC TOXICITY

The critical range of N,N-dimethylurea causing mortality in the creek chub, Semotitus atromaculatus, was 7000-15,000 mg/ℓ (Gillette et al., 1952). The lower level defines the concentration of N,N-dimethylurea that was tolerated by all fish (n = 4) for a period of 24 hours. The upper limit is the minimal concentration causing 100% mortality within 24 hours of exposure.

Pertinent data regarding the effects of N,N-dimethylurea on chronically exposed organisms or aquatic plants were not located in the available literature. No data on residues of N,N-dimethylurea in aquatic organism or the aquatic environment were located.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

No existing guidelines or standards were located for N,N-dimethylurea.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of N,N-dimethylurea were not located in the available literature.

8. RISK ASSESSMENT

Sufficient data are not available to determine the extent and possibility of human risk due to exposure to N,N-dimethylurea. No information is available regarding the carcinogenicity, mutagenicity or chronic toxicity of this compound. N,N-Dimethylurea was not teratogenic to rats in a study by Von Kreybig et al. (1969), but the experimental methods and results were not reported in adequate detail by the authors.

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Weast, R.C., Ed. 1980. CRC Handbook of Chemistry and Physics, 61st ed. CRC Press, Inc., Boca Raton, FL. p. C-621.

APPENDIX: LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
EPCASR
Chemical Industry Notes

Most of these searches were conducted in February 1983; a few were conducted March-May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. TLVs: Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981). Cincinnati, OH. p. 486.

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